Design and in vitro evaluation of a novel controlled onset extended-release delivery system of metoprolol tartrate

Jaber Emami* and Mohammad-Reza Kazemali

Abstract

Blood pressure rises rapidly upon awakening and maybe responsible, in part, for the increased incidence of myocardial infarction and stroke during the morning hours. The aim of the present study was, therefore, to develop a novel chronotherapeutic formulation of metoprolol tartrate (MT) for night time dosing providing maximum effect in the morning hours. Core tablets contained MT, sodium chloride, lactose, Avicel® and starch. Powders were mixed, sieved and directly compressed in to tablets using a single punch tablet machine. Core tablets were then coated with 5 or 10% hydroxypropyl methylcellulose as swelling layer and subsequently outer membrane with the mixture of various ratios of Eudragit® RS to RL at different coating levels 5, 10, 15% as semi-permeable water insoluble outer coat by conventional pan-spray method. The best formulation with regard to release behavior was chosen and subjected to further release studies in various rotational speed and pHs. Both lag time and release rate were dependent on the coating levels and the osmotic pressure of dissolution medium. A linear relationship between lag time and outer coating levels was observed. The lag time was prolonged with an increase in the coating levels. Both diffusion and osmotic pumping effect were involved in drug release from the device. Significant increases in drug release behavior was not observed using dissolution medium with various pH and different agitation rates. It was found that the release rate was independent of pH, rotational speed and gastric motility and may not be altered due to changes of pH and peristaltic movement along the GI tract.

Keywords: Metoprolol tartrate; HPMC; Eudragit; Osmotic pump; Pulsatile release

INTRODUCTION

Oral drug delivery remains the most popular and convenient form of administration of drug to patients. Among oral modified-release systems, controlled drug delivery systems have received remarkable attention. In recent years, temporal and spatial control of drug delivery has been of interest to achieve improved drug therapies (1). Rhythmicity in the physiology of medical conditions is the rational for chronopharmaceutical drug delivery to optimize treatment outcomes and to improve drug therapies (2,3). Many chronic and acute medical conditions exhibit prominent circadian patterns of symptom manifestation and severity (4). Among the many examples are allergic rhinitis, asthma, and peptic ulcer disease, all tend to worsen overnight (5). Many cardiovascular events including myocardial ischemia, angina pectoris, acute myocardial infarction, sudden cardiac death (6,7), ventricular arrhythmia (8), stroke (9), and hypertensive crises (4) all are most frequent in the morning. Blood pressure follows circadian rhythms both in normotensive and hypertensive persons. Blood pressure is usually lowest during sleep, rises toward the end of the sleep cycle and upon waking and reaches its peak in the late morning or early afternoon and may be responsible in part for the increased incidence of myocardial infarction and stroke during the morning hours (10,11). Thus, there is growing interest in how to best tailor the treatment of hypertensive patients according to the circadian blood pressure pattern (12). Hence, the major objective of chronotherapy for hypertension is to control hypertension more optimally during morning hours when blood
pressure is highest. This goal can be achieved by designing a chronopharmaceutical drug delivery system which delivers the drug in accordance with the circadian rhythms of the hypertension. The formulation strategies involve designing an appropriate system to provoke drug release from the formulation in a time dependent manner and provide sustained release following the delay period. In most cases special drug delivery technology must be relied upon to synchronize drug concentrations to rhythms in disease activity. The strategies are mainly involved osmotic control (13,14), hydrophilic and/or hydrophobic layers coating a drug-loaded core (15,16), and swellable or erodible plugs sealing a drug containing insoluble capsule body (16,17). One of the technologies which could be incorporated in controlled onset extended release drug delivery system is osmotically control drug delivery system that utilizes osmotic pressure as the energy source for the controlled delivery of drugs (18). Drug release from such systems is independent of pH and GI motility to a large extent and characteristics can be easily adjusted by optimizing the parameters of delivery system (19,20).

Metoprolol tartrate (MT) is a cardioselective beta blocker lacking of intrinsic sympathomimetic activity having little or no membrane stabilizing activity. It has been effective in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction and heart failure (21).

In view of the circadian rhythm of cardiovascular diseases, time-controlled release formulation of MT with lag time has been prepared by coating the conventional core tablet with coat granulations using hydrophilic polymers (22), ethyl cellulose (23), layering of the inner pellets with drug, a swellable layer of doshion resin and water-insoluble polymer membrane with ethyl cellulose (24), or Eudragit® RS (13).

The aim of the present study was, therefore, to develop a novel chronotherapeutic formulation of metoprolol for night time dosing releasing higher concentration during the morning hours to provide maximum effect followed by maintenance of plasma levels for the rest of the day. This system was designed based on osmotic technology which consisted of a core tablet-containing drug and osmagent, an inner swelling hydroxypropyl methylecellulose (HPMC) layer and an outer rate controlling semipermeable polymer membrane containing Eudragit® RS and RL mixture. Dosage forms were coated with different amount of HPMC and different ratios of Eudragit® RL and RS at different coating levels to provide desire drug release model to fulfill the chronotherapeutic requirements of hypertension.

To assure a reliable pH independent performance of the formulation, release studies of the optimized formulation was conducted in media of different pH. Since besides simple diffusion, osmotic pumping mechanism may also contribute in drug release from developed chronopharmaceutic system, the mechanism of drug release from the optimized formulation was also elucidated.

**MATERIALS AND METHODS**

**Materials**

Following materials were used in this study: Metoprolol hydrochloride (Alborz Daru Co., Iran), Eudragit® RS and RL (Rohm Pharma, Germany), Hydroxypropyl methylecellulose E5 (Methocel E5, Colorcon Limited, UK), Sodium chloride (Merck Co., Germany), Lactose (Fast Flo, Foremost Food Company, San Francisco, Calif. 94104), microcrystalline cellulose (Avicel® pH 101, FMC, Biopolymer, USA). All other chemicals used were of reagent grade.

**Drug analysis**

MT was analyzed with ultraviolet spectrophotometric method at \( \lambda_{\text{max}} \) 275 nm (UV mini/420 Shimadzo, Japan). Calibration curves were prepared in methanol, distilled water, hydrochloric isotonic buffer pH 1.2, isotonic phosphate buffer pH 6.8, isotonic phosphate buffer pH 7.4, or sodium chloride solutions in the concentration range of 5-100 µg/ml. Correlation coefficients were always found to be greater than 0.999 for all media and no interference of additives used in formulation was observed.
Preparations of core tablets

The core tablet was composed of 100 mg MT, 75 mg lactose, 150 mg Avicel®, 100 mg sodium chloride, 70 mg starch and 5 mg magnesium stearate. MT was mixed with all the excipients and sieved through a 120 mesh screen (open size: 125 µm) and directly compressed into 500 mg tablets using shallow concave punches of 9 mm in diameter on a single punch tablet machine (KS 43373-202 Kiliian Co, GMBH, Koln-Niehl, Germany). Tablet hardness was monitored using a tablet hardness tester (Model T.B324-Pharmatest, Germany). Compressed core tablets were evaluated for appearance, weight variation, content uniformity, hardness, friability (Erweka, T.A.P, Germany), and disintegration time (Pharma-Test PTZE) to meet the predetermined criteria suitable for coating. Before initiation of formulation development, compatibility of MT with different excipients used for the preparation of core tablet was tested using the technique of differential scanning calorimetry (Mettler, DSC-30, TC11, Switzerland) and IR spectroscopy (Perkin Elmer, TGA 7, USA).

Coating of swelling agent and outer Eudragit® membrane

The composition of coating solution used for coating of MT tablet is given in Table 1. The ratio of Eudragit® RS to RL was different (100:0, 25:75, 50:50, 75:25, 0:100) while the total amount of Eudragit® polymer was always constant (3%) in the dispersion formulation. The HPMC layer was performed at 5 and 10% levels and the Eudragit® levels of 5, 10, and 15%. The entire design is shown in Table 2. Various components of the coating solution/dispersion were added in sequential manner. For swelling layer, HPMC (3 g) was first dispersed into 75 ml of ethanol. Cold water containing PEG 400 was then added to 100 ml. For outer membrane, Eudragit® RL/RS and dibuthyl phthalate was dissolved sequentially in required ethanol. To this was added the aqueous dispersion of PEG 6000 and microtalc already prepared. The component added first was allowed to dissolve or disperse before the next component was added. The coating operation was performed in a conventional laboratory model stainless steel, 20 cm, pear-shaped, baffled coating pan (Isfahan, Iran).Core tablets of MT (150 tablets) for HPMC coating or HPMC coated MT tablets (25 tablets) along with 50 filler tablets (tablets made using 7 mm round standard concave punches containing Avicel®, starch, dibasic calcium phosphate, magnesium stearate, and colloidal silicon dioxide) for outer Eudragit® coating were placed in the coating pan. Initially pan was rotated at low speed (2-5 rpm) and heated air was passed through the tablet bed. After being warmed, core tablets were spray-coated with either the swelling layer or outer membrane. The pan speed was 30 rpm and the coating solution was manually sprayed on the surface of the tumbling tablets with a spray gun. The inlet air temperature was 30-35 ºC and the manual coating procedure used was based on intermittent spraying and drying techniques. The coat weight and thus the thickness were controlled by the volume of coating solution consumed in the coating process. Coated tablets were weighed periodically to monitor changes in weight. The coating level in % (w/w) was determined from the weight gain of 20 tablets, which were coated at the same time, divided by the initial tablet weights. The tablets were dried at 50 ºC for 5 h to remove residual solvent after coating. Coating was continued until desired weight gain was obtained on the active tablets. The surface morphology of the tablets was smooth and uniform in appearance.

Table 1. Coating composition for HPMC layer and Eudragit® film.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Coating solution (%)</th>
<th>Coating suspension (%)</th>
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<td>HPMC E5</td>
<td>3</td>
<td>-</td>
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<tr>
<td>PEG 400</td>
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</tr>
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<td>Eudragit® RS and RL</td>
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<td>Dibuthyl phthalate</td>
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<td>PEG 6000</td>
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<td>Ethanol</td>
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Table 2. Coating levels of HPMC layer and Eudragit® film.

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<th>Formulation</th>
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<th>Eudragits® (%)</th>
<th>Eudragit® coating level (% weight gain)</th>
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<td>H10(S0L100)15</td>
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<td>15%</td>
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</tbody>
</table>

*a; HPMC, b; Eudragit® RS, c; Eudragit® RL.

*Dissolution was so fast and hence the release profile is not illustrated in Fig. 1.

In vitro drug release test

The developed formulations of MT (n = 6) were subjected to release studies using USP II dissolution apparatus (paddle method, Erweka, DT700) at 100 rpm and 900 ml distilled water as dissolution medium maintained at 37 ± 0.5 °C. The 4 ml samples were withdrawn at different time intervals and replaced with medium of the equal volume. The dissolution samples, after filtration through 0.45 µm nylon membrane filters were analyzed using validated spectrophotometric method as described earlier.

After analyzing the drug content in the dissolution samples, corrections were made for the volume replacement and the graph of cumulative percentage of drug release versus time were plotted.

Release profiles were compared using dissolution efficiency (DE) which was calculated using following equation:

\[
\%DE = \frac{\int \frac{y}{y_{100}} \, dt}{y_{100}} \times 100
\]
where, $y_t$ is percent of drug dissolved at any time $t$, $y_{100}$ denotes 100% dissolution, and the integral represents the area under dissolution curve between time zero and $t$ (25). The time $t$ in this study was 3 and 6 h. One way analysis of variance was performed to check whether there is significant difference among the different formulations. The developed formulations of MT were first subjected to release studies in water.

In addition, the optimized formulation was subjected to various tests as follows:

**Effect of pH, rotational speed and osmotic pressure on drug release**

In order to study the effect of pH and to assure a reliable pH-independent performance of the developed formulations, release studies of the optimized formulation was conducted in media of different pH including hydrochloric isotonic buffer pH 1.2, isotonic phosphate buffer pH 6.8, and isotonic phosphate buffer pH 7.4.

To study the effect of agitational intensity, release studies of optimized formulation were carried out in dissolution apparatus in water at various rotational speeds of 50 and 100 rpm.

In order to confirm the mechanism of drug release, release studies of optimized formulation were conducted in solutions containing different concentrations of sodium chloride producing osmotic pressure of 34, 68, 102, and 137 atm. Knowing the osmotic pressure, the molar concentration of sodium chloride was calculated using following equation:

$$ \pi = 1.86CRT $$

where, $\pi$ is the osmotic pressure (atm), C is the molar concentration of solute, R is the gas constant (0.08 l.atm/mol.k), and T is the absolute temperature.

Release profiles of optimized formulation subjected to various conditions as described above were compared using model independent pair-wise approach, which included the calculation of similarity factor, $f_2$.

$$ f_2 = 50 \times \log \left( 1 + \left( 1 / n \right) \sum_{i=1}^{n} \left( R_i - T_i \right)^2 \right) + 50 $$

where, $T_i$ and $R_i$ represent the average percentage of drug released from the three test tablets and three reference tablets at the $i^{th}$ time point, respectively, and n is the number of time points tested. The two release profiles were considered to be similar if $f_2$ value was greater than 50 (between 50 to 100). For the calculation of $f_2$ values only one data point was taken into consideration after 85% of the drug was released (25).

**Release kinetics and mechanism**

In order to evaluate the drug release kinetics and mechanism, the release profiles were fitted into zero order kinetics (equation. 4), first order kinetics (equation. 5), Higuchi model (equation. 6), and Hixson-Crowell model (equation. 7) as indicated below (25).

$$ Q = Q_0 + k_0 t $$

$$ \ln(Q_0 - Q) = \ln(Q_0) - k_1 t $$

$$ Q = k_1 t^{1/2} $$

$$ (Q_0 - Q)^{1/3} = Q_0^{1/3} \times k_{hc} t $$

where, $Q_t$ is the amount of drug released at time $t$, $Q_0$ is the initial amount of the drug in tablet, $Q_i$ is the initial amount of drug in the solution (Y intercept), and $k_0$, $k_1$, $k_h$, and $k_{hc}$ are release rate constants for zero order, first order, Higuchi model, and Hixson-Crowell equations, respectively (25).

A more comprehensive and simple equation, power law, was applied to elucidate the mechanism of drug release from developed formulations.

$$ M_t / M_\infty = K(t - T)^n $$

where, $M_t$ and $M_\infty$ are the absolute cumulative amounts of drug released at time $t$ and infinite time, respectively; $K$ is a constant incorporating structural and geometric characteristic of the device; $T$ is lag time, and $n$ is the release exponent, indicative of the mechanism of drug release. $n = 0.45$ indicates diffusion-controlled drug release (Fickian) and $n = 0.89$ indicates swelling-controlled drug release (Case II). Values of $n$ between 0.45 and 0.89 can be regarded as an indicator for the superposition of both phenomena (anomalous transport). Values which are greater than 0.89 indicate super case II transport (25).
**Statistical analysis**

Experimental results were expressed as mean ± SD values. One-way analysis of variance (ANOVA) was used to assess the differences between dissolution rate constants and dissolution efficiencies. Student-t-test was used to compare two means where appropriate. *P* value of less than 0.05 was considered significant.

**RESULTS**

**Drug analysis**

As explained earlier, MT was analyzed with ultraviolet spectrophotometric method. The assay was linear in the concentration range of 5-100 µg/ml as correlation coefficients of calibration curves were always found to be greater than 0.999 for all media and no interference of additives used in formulation was observed.

**Physical characteristics of core tablets**

The results of physical characteristics of prepared core tablets of MT showed uniform thickness throughout. No significant difference in the weight of individual formulations from the average value was observed and variations were within the limits. The drug contents in the core tablets were also within the limit of 97.0-104.2% with a coefficient of variation 2.09%. The mean hardness of tablets was 70.9 ± 4.56 N and the friability was 0.79%.

**Effect of coating levels on drug release**

Drug release profiles of tablets with various coating levels of HPMC and Eudragit® RL or Eudragit® RS alone or in combination are shown in Fig. 1 and Fig. 2. DEs and lag times were calculated and used for comparison and statistical analysis of the release profiles, but to avoid elongation of the article the raw data are not given in the result section.

**Release kinetics and mechanism**

Inspection of drug release profiles, sum of squared residuals, comparative correlation and coefficients revealed that the release kinetics of majority of formulations followed either zero or first order kinetics, while few could be fitted in the Hixson-Crowell models. None of the formulation release kinetics followed Higuchi model. Results also suggested that the vast majority of the formulations conformed to the case II mechanism; while only two formulations followed super case II behavior.

![Fig. 1. Drug release profiles of tablets with 5% HPMC coating levels and different coating levels of Eudragit® RL or Eudragit® RS alone or in combination.](image-url)
Controlled onset extended-release delivery system of metoprolol

Effects of pH and rotational speed on the drug release behavior

Drug release behavior in media with various pH and under different rotational speeds are shown in Fig. 3A and B, respectively. The similarity factor ($f_2$) was used to evaluate the drug release behavior between different pH and different rotational speeds. The $f_2$ of dissolution curves in isotonic buffer pH 1.2, isotonic phosphate buffer pH 6.8, and isotonic phosphate buffer pH 7.4, and different rotation speed compared to dissolution profile in water were 82.9, 91.7, 64.9, and 62.7, respectively.

Osmotic pumping effect

The drug release profiles in sodium chloride solutions with different osmotic pressures are shown in Fig. 3C.

IR spectroscopy

The IR spectra of MT and excipients are demonstrated in Figs 4a to 4e. The IR spectrum of MT (Fig. 4a) showed characteristic bands at 3350 cm$^{-1}$, 1613 cm$^{-1}$, and 1245 cm$^{-1}$ due to -NH, C=O and C-O stretching vibration, respectively. The peaks of 1512 cm$^{-1}$, 1112 cm$^{-1}$ and 800 cm$^{-1}$ are for aromatic ring, alkyl aryl ether linkage and 1,4-disubstitution of benzene ring. Fig. 4e shows the IR spectrum of MT physical mixture with lactose, starch, and Avicel®.

Differential scanning calorimetry

Thermal analysis was conducted to establish the existence of any possible interaction between the drug and tablet excipients. MT thermogram (Fig. 5A) demonstrated a sharp characteristic endo-
thermic peak at 125 °C which corresponds to its melting temperature. The thermograms of lactose (Fig. 5B) displayed an endothermic peak near at 214 °C due to decomposition of this compound. No sharp dehydration endotherm at about 140 °C in dehydrated sample was observed. The DSC thermograms of starch (Fig. 5C) showed a shallow endotherm about 60 °C which lies in the gelatinization range of the starch. The DSC thermograms of Avicel® (Fig. 5D) showed a broad and shallow transition over the temperature range of 60-140 °C probably due to the evaporation of adsorbed water.

Fig. 3. Drug release profiles of optimized formulation assigned as H10(S75L25)10 A; in dissolution media with different pH, B; under different rotational speed, and C; in dissolution media with different osmotic pressure.

Fig. 4. IR spectra of a; metoprolol tartrate, b; lactose, c; starch, d; Avicel®, and e; MT physical mixture with lactose, starch, Avicel®.
DISCUSSION

The dosage form developed consisted of a tablet core of MT along with other conventional excipients. Sodium chloride was used as osmagent in the formulations causing osmotic pressure. Fabricated tablets were optimized in terms of membrane thickness and composition. The core was surrounded by a swelling layer and an outer rate controlling membrane. Tablet cores containing MT were coated with a low-viscosity HPMC as a permeable and swellable polymer at 5 and 10% weight gain which was subsequently spray coated with a mixture of Eudragit® RS and RL with different ratios as insoluble polymers at 5, 10, and 15% weight gain. A 3% polymer solution/suspension was used in the coating formation in order to minimize tablet-to-tablet variation in coating thickness. Uniform application of a given amount of polymer was best accomplished with a larger number of coatings using a more dilute solution. The film former polymers were plasticized with either PEG 400 or dibutyl phthalate to improve the stability of the film by increasing the flexibility of the membrane. The inclusion of a suitable plasticizer in polymeric films lowers the glass transition temperature of the polymer and alters physical properties such as flexibility, hardness, tensile strength, and elasticity. Eudragit® RS contains 33 moles of quaternary ammonium groups per mole of polymers. Because the number of hydrophilic quaternary ammonium groups of Eudragit® RL is two times higher than that of Eudragit® RS, the permeability of Eudragit® RL is greater than that of Eudragit® RS.

In operation, the core imbibes water from surrounding environment through the membrane. After exposure to the aqueous fluids, the penetration of water into the inner coat and core tablet begins. The time required for permeation of water through the Eudragit® film, swelling of HPMC layer, dissolution of sodium chloride and drug and initiation of osmotic pressure inside core tablets determine the lag time of the formulations. Later, gradually the dissolved drug is released through the pores and cracks created after the expansion of the membrane and leaching of water-soluble additive (PEG 6000). The lag duration and release rates depend on the amount of inner and outer polymers and Eudragit® RL to RS ratios. Therefore, formulation development involved different trials with HPMC, two types of Eudragit® and various coating levels.

The results of the release experiments indicated that the lag time was extended with the increase in inner and/or outer coating levels while DE was decreased. By comparison of dissolution profiles illustrated in Fig. 1 with Fig. 2, it is clearly evident that the drug release decreased and the lag time was extended with the increase in coating levels of HPMC. It is speculated from related figures that when the content of Eudragit® RS in the outer coating level increased, drug release declined and more near linear relationship between lag time and outer coating level was observed. Similar to HPMC,
by increasing Eudragit® coating levels both the lag time and drug release rate were decreased (Fig. 1 or Fig. 2). Tablets with Eudragit® RL alone in their outer membrane (profiles are not shown in Fig. 1) released their entire content within 5 h with very short lag durations. The formulation H10(S75L25)10 met the objective of this study. The lag duration achieved was about 5 h and entire drug content was released during 12 h.

The $f_2$ values of dissolution curves in isotonic buffer pH 1.2, isotonic phosphate buffer pH 6.8, isotonic phosphate buffer pH 7.4 and under different rotational speed compared to dissolution profile in water were higher than 50. Two dissolution profiles are thought to be statistically similar if the $f_2$ value is above 50. Therefore, no significant differences in drug release behavior were observed in media with different pHs or under different rotational speeds. Therefore, it can be supposed that the in vivo release properties of the pulsed-release tablet will not change due to changes of pH along the GI tract and GI tract mobility, which accords with the time-control character.

It is evident that the release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core formulation. For controlling the drug release from these systems it is important to optimize the osmotic pressure gradient between inside compartment and external environment. It is possible to achieve and maintain a constant osmotic pressure by maintaining a saturated solution of osmotic agent in the compartment (15). If a drug does not possess sufficient osmotic pressure, an osmoagant like potassium or sodium chloride can be added to the formulation. It is possible to confirm the contribution of osmotic pressure in drug release from osmotic system by conducting the release studies in media of different osmotic pressure (26). The release rates obtained was plotted against the osmotic pressure difference across the device membrane. Using this approach release of potassium chloride from controlled porosity osmotic pump was studied in aqueous media of different osmotic pressure and an inverse relationship was found between the osmotic pressure and release rates (27,28). Similarly in the current study a negative linear relationship between the osmotic pressure and release rates was observed confirming osmotic pressure driving force in the system. With the increase of osmotic pressure in the dissolution medium, the lag time was also prolonged proportionally. These results suggest that the osmotic pressure difference across the membrane plays an important role in drug release behavior. There have been several papers describing, besides simple diffusion, osmotic pumping mechanism also contributes to the drug release from film coated devices (16-18). The diffusional contribution is derived from the fact that the membrane is not perfectly semipermeable, and therefore a portion of drug is released by diffusion through the pores in the coating. This indicates that diffusion, membrane swelling and osmotic pressure are involved in the mechanism of drug release.

IR spectroscopy was performed for the pure drug and powder mixtures to detect any sign of interaction which would be reflected by a change in the position or disappearance of any characteristic stretching vibration of the compound. In the physical mixture, the bands observed at 3350 cm$^{-1}$ became deeper and wider due to the strong stretching bonds observed in other excipients (Figs. 4b to 4d) in this region. However, distinctive bands observed for MT at 1613 cm$^{-1}$ to 800 cm$^{-1}$, with the absence of any additional peaks, are visible and not overlapped with excipient bands indicating that there was no interaction between the drug and other ingredients.

A comparison was made between the DSC endotherm positions of pure drug and its physical mixture with excipients. It was observed that major peak positions for the drug in physical mixture was totally in compliance with that of the pure drug indicating the absence of drug-polymer interactions (Fig. 5). MT thermogram demonstrated a sharp characteristic endothermic peak at 125 °C signifying that MT used was in pure crystalline state not changing in physical mixture. Disappearance of the lactose decomposition peak may indicate solubilization of this agent in melted drug and other excipients.
CONCLUSION

A pulsed-release system with lag-times consistent with the requirements for chrono-pharmaceutical drug delivery was achieved based on an osmotic agent and swelling layer, which induce perforation of the semi-permeable coating material. After the formation of fractures the drug was released quickly. The osmotic active agent and swelling layer are proved to be essential for the fast drug release phase. Drug release mechanism of this device involved both diffusion and osmotic pumping effect, but the latter was more important. This system can be useful to realize highly improved pharmacotherapy according to the concept of chronotherapy by usual dosing regimen. In further studies the properties of the pulsed-release system will be compared to the mechanical properties of free film. In addition, the pharmacological effect of this pulsed-release system on relieving asthma symptoms will be investigated.

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